Flexible Optoelectronic Devices for Neural Recording and Stimulation

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Our ability to understand and treat debilitating neurological conditions such as Parkinson's disease, spinal cord injury or major depression is largely limited by the lack of materials and devices that can seamlessly interface with the neurons and restore or bypass the malfunctioning neural circuits (Normann 2007; Cogan 2008; Gilja 2011). The technology employed in deep brain and spinal cord stimulation devices used by clinicians to treat Parkinson's disease and chronic pain dates back to 1970s (Gildenberg 2005; Kringelbach 2007). Even the cutting-edge experiments allowing tetraplegic patients to control robotic aids (Hatsopoulos and Donoghue 2009; Hochberg 2012) depend on devices invented over 20 years ago (Campbell 1991). These devices do not take into account the fundamental material properties of neural tissue and, consequently, suffer from reliability issues that reduce their long-term effectiveness (Lee 2005; Polikov 2005). Flexible organic and hybrid electronics offers a compelling solution to the elastic and surface chemistry mismatch between neural probes and neural tissues, while enabling novel approaches for neural interrogation. Recent developments in materials chemistry and fabrication methods make flexible electronics ripe for tailored, bio-integrated neuroprosthetics. Here I review the spectrum of neural recording and stimulation technologies and highlight the role of flexible electronics and optoelectronics at the frontier of neural engineering.

BACKGROUND

Neural systems exchange information in form of action potentials – voltage spikes that propagate along neuronal membranes, and fluctuations in local field potentials (LFPs) averaged across a neuronal subnetwork or even an entire structure within the nervous system. Devices for neural recording and stimulation interact with neural tissues with different degrees of precision and invasiveness (Buzsáki 2012). For example electroencephalography (EEG) is performed non-invasively through the skull and thus offers a low-resolution map of smoothed field potentials associated mainly with the neural activity of the whole cortical surface. Electrocorticography (ECoG) devices placed directly onto cortical surface allow for higher temporal and spatial resolution and are routinely used in clinic for localization of seizure loci in epilepsy patients. The detailed mapping of the neural activity, however, is clinically relevant in structures beyond superficial cortical layers such as in deep brain regions (*e.g.* subthalamic nucleus in Parkinson's patients), spinal cord and peripheral nerves (*e.g.* in trauma or chronic pain patients). Moreover, many neurological disorders are associated with abnormal activity of specific types of neurons and hence single-neuron resolution is essential to the development of effective therapies. Consequently, here I will focus on invasive penetrating neural recording devices, designed to interface with individual cells in a particular region of the nervous system.

Similarly to neural recordings, neural stimulation, employed in neuroprosthetics offers varying degrees of precision and invasiveness. Non-invasive transcranial magnetic stimulation (TMS) allows for interrogation of cortical circuits via initiation of local flows of ions, which are hypothesized to yield changes in LFPs (Allen 2007; Ridding and Rothwell 2007). However there currently is no strategy for extending this approach to deep brain regions or targeting it to specific neuronal types due to the non-specific nature and the limited penetration depth of the

low frequency magnetic fields used in TMS. In deep brain stimulation (DBS), an approved treatment for Parkinson's and essential tremor patients, high voltage pulses (1-10 V) as compared to membrane voltages (~ 30-100 mV) or LFPs (~ 1-5 mV) are employed to stimulate the entire volume of neural tissue surrounding the electrodes (Perlmutter and Mink 2006). While the DBS therapeutic ability is well documented, its underlying mechanisms remain unclear as both, electrically-induced excitation and inhibition of neural activity have been proposed (Kringelbach 2007). Furthermore, the non-specific interrogation of large tissue volume often yields undesirable side effects such as depression and compulsive behaviors among others (Frank 2007; Temel 2007). Epidural electrical stimulation in the spinal cord of chronic pain patients is essentially equivalent to DBS, with a key difference of the electrode leads being placed on top of the dura (thin barrier isolating nerves from other tissues) rather than in the depth of the neural tissue.

With the development of optogenetics it became possible to excite and inhibit specific neuronal types with millisecond precision (Boyden 2005; Zhang 2007). This method employs genetic targeting of light-sensitive proteins, opsins, from algal, archeal and bacterial origin to enable neuronal sensitivity to a variety of visible light wavelengths. Opsins can be approximately divided into excitatory (used for evoking action potentials, e.g. sodium and calcium channel channelrhodopsin 2, ChR2) and inhibitory (used for inhibiting action potential firing, e.g. modified cloride pump halorhodopsin, eNpHR3.0 and modified proton pump archearhodopsin, eArch3.0) (Zhang 2011). While optogenetics is a powerful tool for scientific investigation of the behavioral correlates of neural dynamics, its genetic and mechanical invasiveness currently impedes its clinical translation (Yizhar 2011). As mammalian tissues are highly scattering and absorptive in the visible range, implantation of optical waveguides or light-emitting devices is necessary for implementation of optogenetics. Thus, optical stimulation technologies face similar materials design and biocompatibility challenges as the tissue-penetrating neural recording and electrical stimulation electrodes.

RELIABILITY CHALLENGES OF IMPLANTABLE NEURAL PROBES

Neural recordings and stimulation devices have been traditionally fabricated out of hard materials with elastic moduli (Young's modulus E ~10s-100s GPa) exceeding those of neural tissues (E ~ kPa-MPa) (Borschel 2003; Green 2008) by many orders of magnitude. For example neural recording and electrical stimulation electrodes (**Fig. 1**) are often based on silicon (silicon MEAs or "Utah arrays" (Campbell 1991; Bhandari 2008), multitrode probes (Kipke 2003; Blanche 2005; Seymour 2011)), silica (cone electrodes (Kennedy 1992; Bartels 2008)) or metals (individual microwires of tungsten, gold, platinum or platinum-iridium alloys; tetrodes and stereotrodes of nickel-chromium alloys (McNaughton 1983; Gray 1995; Jog 2002)). Similarly, optical stimulation in optogenetic experiments is most routinely performed with standard commercially available silica optical fibers (E ~ 50-90 GPa) implanted directly into neural tissue.

It is hypothesized that this mismatch in stiffness contributes to the tissue damage and the resulting encapsulation of devices in dense scars composed of glial cells, which leads to a decrease in recording quality (Lee 2005; Polikov 2005). It is reasonable to assume, that the initial impact of the probe insertion produces certain amount of damage as well since the cells on the way of the implant are destroyed or misplaced. This is supported by the commonly observed

improvement in recording quality approximately two weeks following the device implantation. However, the signal-to-noise ratio (SNR) and the total number of recorded neurons then decay steadily over the course of the implant lifespan. Several mechanisms have been proposed in attempt to explain the neuronal death and the glial scarring contributing to the probe failure. As neural probes are generally at least partially fixed to the skull/vertebrae their motion is constrained, while the neural tissues may shift by tens to hundreds of micrometers due to movement, heart beat and respiration (Britt and Rossi 1982; Muthuswamy, Gilletti et al. 2003). This micromotion of soft neural tissues around the hard implants is thought to introduce additional tissue damage. The disruption of glial networks by the devices larger than an average cell (> 10 μm) may yield increased astrocytic and astroglial responses leading to thickening of

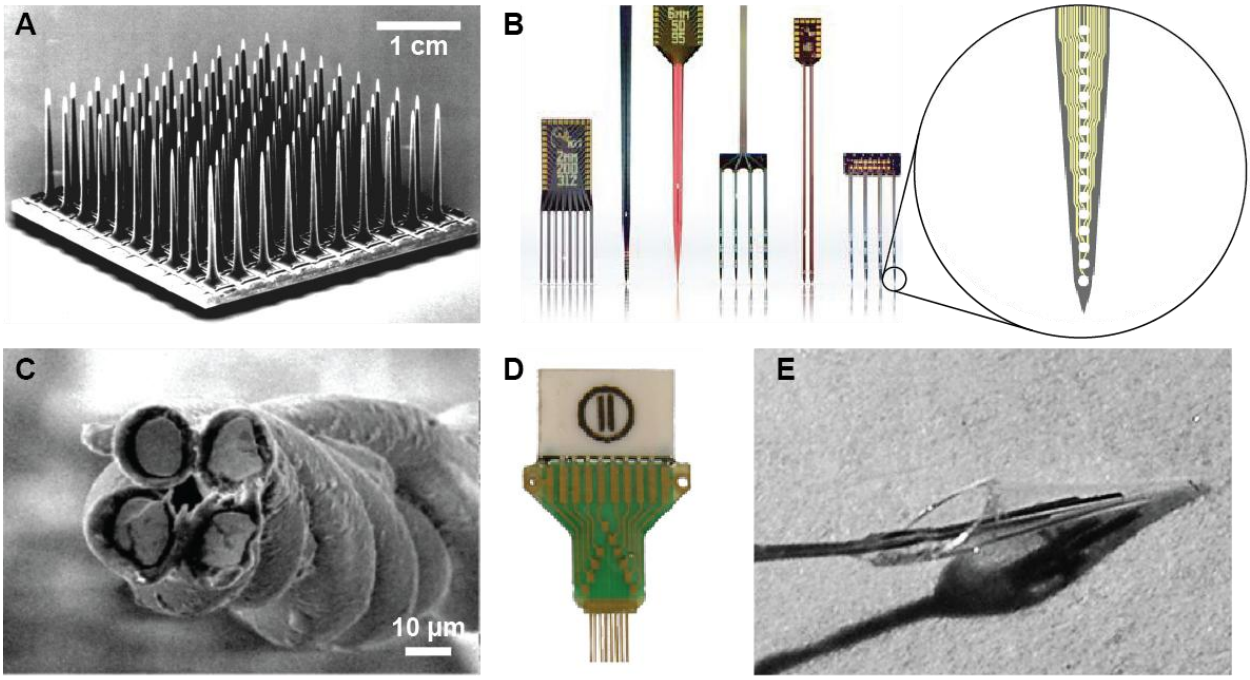

Figure 1. Examples of single unit and LFP recording devices commonly used in research setting. (A) Silicon multielectrode array (Blackrock Inc.). (B) Silicon multitrode probes (Neuronexus Inc.) Inset shows the detailed structure of the recording electrodes. (C) Tetrode microwire bundle (University of Queensland). (D) Tungsten microwire array (Tucker-Davis Technologies Inc.) (E) Silica cone electrode (Neural Signals Inc.)

the scar around the device. The devices with particularly sharp edges have also been shown to be disruptive to the blood-brain barrier, which induces an inflammatory response raising glial activity (Saxena 2013).

Flexible organic and hybrid electronics and optoelectronics thus offer unique opportunities to address the elastic, geometric and chemical compatibility challenges of neural recording and stimulation devices paving the way for minimally invasive neuroprosthetics.

NEURAL PROBES ON FLEXIBLE SUBSTRATES

Combining traditional metal and semiconductor technologies with flexible substrates provides a first transitional step towards stealthy bio-inspired neural probes. Over the past decade polymer substrates have been employed as a backing for metal and silicon-based neural recording electrodes. Using lithographic MEMS-inspired processing, electrode arrays have been developed atop of silicone resins (poly(dimethylsulfoxane) (PDMS)), polyimide and parylene C to name a few (Stieglitz 2009; Lacour 2010; Viventi 2011; Kim 2013). As these devices exhibit extremely high flexibility and ability to conform to the complex landscape they found immediate applications in high-density microstructured cortical arrays (micro-ECoG or μECoG) and nerve cuffs.

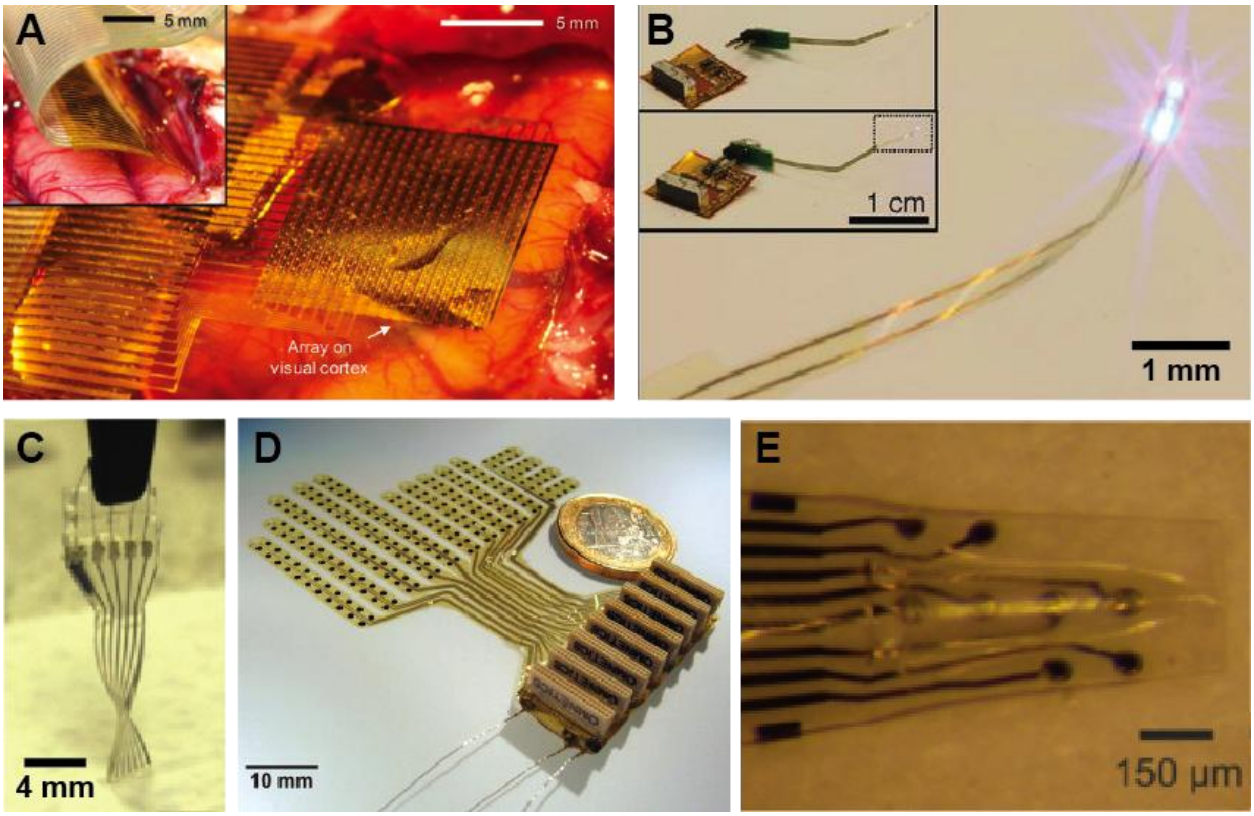

Figure 2. Examples of neural probes on flexible substrates. (A) Microprinted high-resolution μECoG array on polyimide substrate for cortical LFP mapping (Viventi 2011). (B) Microprinted optoelectronic device on a polyimide substrate incorporating a gold electrode, a GaN-based light-emitting diode, a silicon photodetector and a resistor for temperature monitoring. For insertion device is adhered onto a silicon microneedle with silk fibroin (Kim 2013). (C) Flexible micro-electrode array on a PDMS substrate (Lacour 2010). (D) Flexible epicortical array on a polyimide substrate (Rubehn 2009) (E) Parylene C sheath electrode (Kim 2013).

Contact printing methods developed by Rogers and colleagues have enabled highly-innovative neural probes. This technology takes advantage of mature semiconductor-based (opto)electronics and combines it with flexible interconnects that enable transfer of several micron-thick circuit elements onto polyimide and silk-fibroin backing (Kim 2010; Kim 2011). Recently, resorbable

microneedles were employed to introduce these flexible and foldable devices into the depth of the brain (Kim 2013).

Meng and colleagues have taken an alternative approach by using a thermal molding process to produce soft cone-electrodes based on parylene C with active electrode pads facing inside the cone. This creative technology relies on earlier findings by Kennedy and colleagues who employed silica capillaries seeded with nerve fragments to attract neuronal growth into the capillary containing an electrode and thus making a truly bio-integrated device (Tooker 2004; Kim 2013).

Despite the recent groundbreaking work by Stieglitz, Rogers, Meng and many others (**Fig. 2**), there still remains a number of challenges in fabrication of neural probes on flexible substrates, including relatively low resolution dictated by contact printing methods, scalability to high number of channels necessary for comprehensive mapping of brain activity, interfacing with optical or drug-delivery elements essential for neural interrogation and potentially cell-type identification. Robust reproducible manufacturing of the probes suitable for use in human patients presents another challenge as MEMS-style processing offers relatively low yield and is currently constrained to standard wafer sizes (several inches as compared to several feet long spinal cord).

SURFACE MODIFICATION AND ENCAPSULATION OF NEURAL PROBES

Materials interfaces between the devices and neural tissues play a critical role in tissue response as well as the quality of neural recording and hence surface engineering provides another important aspect of neural probe design. With their tunable chemical properties and low elastic moduli organic materials offer a compelling toolbox for engineering of intimate electrically and optically active interfaces between the neurons and the neural probes.

Polymers such as (poly(3,4-ethylenedioxythiophene), PEDOT (Richardson-Burns 2007; Blau 2011; Ludwig 2011), polylysine (Hai 2010; Boehler 2012) and polypyrrole (George 2005; Abidian 2010) have been shown to boost the reliability and SNR of neural recording electrodes by promoting cell adhesion and reducing the impedance of the equivalent circuits between the devices and the neuronal membranes.

Hydrogels based on polymers and polymer blends of natural (agarose, alginate, xyloglucan, hyaluronan, methylcellulose, chitosan and matrigel) and synthetic (methacrylate, polyethylene glycol (PEG), poly(vinyl alcohol), poly(acrylic acid)) origins currently constitute a dominant materials platform for neural regeneration scaffolds (Jhaveri 2008; Nisbet 2008; Frampton 2011; Hanson Shepherd 2011; Seliktar 2012; Shin 2012) and have recently found application in surface modification of neural probes (Jun2008; Lu 2009; Kim 2010). The advantages of hydrogels include elastic moduli comparable to those of the neural tissues and high permeability to nutrients and oxygen. However, the electrical and optical properties of these soft gels have not yet been engineered for improved neural recording and stimulation. Consequently their application in neural probe engineering has been restricted to providing low-modulus, biocompatible buffers, which could possibly reduce the damage produced by the otherwise hard devices during micromotion.

Encapsulation is another form of surface modification routinely used during implantation of flexible neural probes into the depth of the tissue. As mentioned above, flexible substrates allow to overcome the elastic modulus mismatch between the electronic or optoelectronic probe and the neural tissue. However, this implies the obvious difficulty of targeting such soft devices to a specific regions of the nervous system, as the bending stiffness is insufficient to allow for straight-line penetration. Consequently, dissolvable encapsulation is used to temporarily stiffen the probe for the duration of surgical procedure. Organic and bio-polymeric materials, such as PEG, sugar, tyrosine-based polymers and silk fibroin are often employed due to their tunable dissolution speed in aqueous environments, versatile chemistry and biocompatibility. While PEG and more recently developed tyrosine-based polymers are employed as temporary structural components of neural probes, silk fibroin has been recently employed as a biocompatible adhesive, which allows to introduce PDMS-backed probes using silicon microneedles, which are retracted shortly following the implantation upon silk fibroin dissolution.

POLYMER AND FIBER INSPIRED NEURAL PROBES

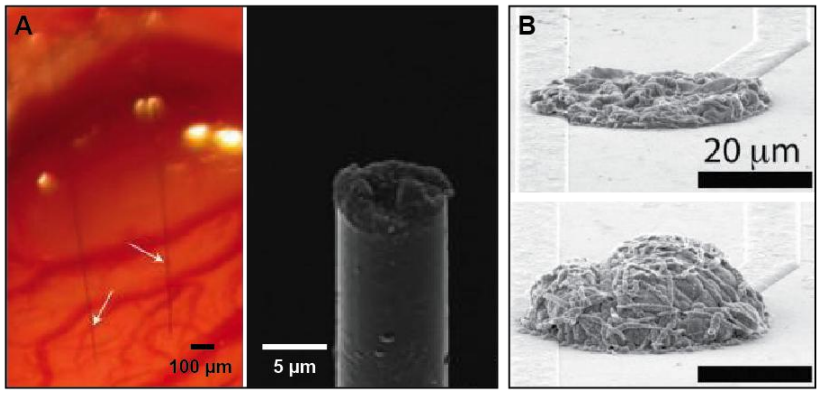

Figure 3. Examples of polymer and organic/inorganic composite neural recording electrodes. (A) Carbon-composite microelectrodes CVD-coated with polyxylene. Tip is electrochemically coated with PEDOT (Kozai 2012). (B) Electrodes coated with electrochemically deposited polypyrrole nanotubes (Abidian 2010).

While flexible substrates provide an essential step towards neural applications of optoelectronics, the observed performance enhancement in neural recording electrodes functionalized with polymer films and the reduced tissue damage by hydrogel-coated probes suggest the possible advantage of an all-organic or hybrid materials platform.

Two decades of advances in materials chemistry have propelled small-molecule organic optoelectronics into commercial applications within the display industry and beyond, however the sensitivity of these materials to environmental moisture and oxygen currently impedes their applications within the body. In contrast, environmentally-stable polymers and polymer composites with tunable chemical and electronic properties and low elastic moduli present a promising materials system for the development of the multifunctional tissue interfaces.

Despite their wide adoption throughout the medical community (orthopedic implants, encapsulation materials for stimulation electrodes, porous scaffolds for soft tissue regeneration, polymers are yet to be fully explored with respect to their applications in optoelectronic neuroprosthetic devices (Green 2008). Pioneering studies by Martin and Kipke among others illustrate the potential of PEDOT, polypyrrole and polymer-carbon composites (Abidian 2010; Kozai 2012) (**Fig. 3**) to solve the elastic mismatch issue of neural recording devices, while

reducing the overall electrode impedance and thus increasing SNR. Furthermore, Capadona and Tyler apply biologically-inspired design principles to create polymer-composites with controllable elastic properties that mimic sea cucumber dermis (Capadona 2008; Harris 2011).

Despite the growing evidence for utility of polymers in neural probe design, a few engineering challenges remain on the way towards universal adoption of these materials systems by the neuroscientists and clinicians. First, polymer probes are primarily fabricated by electrospinning, chemical vapor deposition, thin-film spin-casting and lithography. The former two methods offer relatively low throughput and require post-synthesis assembly steps if multiple electrodes are desired, which is true for the majority of neuroprosthetic applications. Furthermore, these methods currently do not allow for integration of optical elements, which are essential for neural stimulation applications within the neuroscience community. While the well-developed lithographic methods allow for integration of multiple functional elements, they are limited by the flat substrate geometry, which is not ideal for applications in deep brain regions.

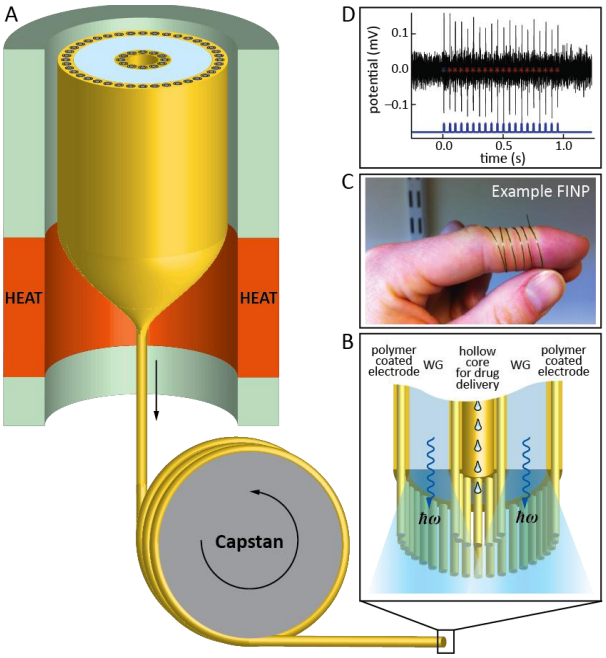

Figure 4. (A) Thermal drawing process (TDP) applied to FINP fabrication. **(B)** Longitudinal cross section of an example FINP for recording, optical stimulation and drug delivery. **(C)** Example FINP. **(D)** Optically-evoked action potentials recorded with a FINP in the medial prefrontal cortex of a transgenic Thy1-ChR2-YFP mouse expressing ChR2 in a broad neuronal population.

Recently, we have explored a thermal-drawing fabrication process (TDP) inspired by optical fiber production. During the TDP a macroscale preform, which can be fabricated using low-end mechanical processing, is drawn into a fiber with microscale features (Varshneya 1994; Goff 2002; Bayindir 2004; Abouraddy 2007) . The lateral dimensions are scaled by as much as 10000 fold using, if necessary, multiple drawing steps, which allows the creation of structures on the nanometer scale without the need for high resolution fabrication technology (Kaufman 2011; Yaman 2011). At the same time the length is stretched by a factor of ~100, yielding hundreds of meters of fibrous devices with a conserved cross sectional pattern. Since TDP faithfully reproduces the cross sectional geometry of the macroscopic preform, it enables the creation of sophisticated multifunctional structures on the microscale. TDP is compatible with a wide range of materials with varying optical and electrical properties, allowing, for example, the combination of waveguide core and cladding materials, conductive polymer composites and low-melting temperature metal microwires within the same device. To date we have applied TDP to a number of test fiber-inspired neural probes (FINPs, **Fig. 4**) ranging from high-channel-count neural recording arrays of arbitrary lengths to multifunctional devices incorporating waveguides, drug-delivery channels and neural recording electrodes. Our preliminary *in vivo* evaluation of

FINPs probes suggest that the TDP may provide a scalable fabrication tool for flexible optoelectronic devices compatible with implantation into a variety of regions of the nervous system. Furthermore, this process may be complimentary to the recent materials discoveries by Martin, Capadona, Kipke and others as it may allow for integration of these innovative polymer systems into multifunctional probes as well as offer a pathway towards their high-throughput production.

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